ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Animec Super Solution for Injection for Cattle
Animec Plus Solución inyectable para bovino (Spain)
Animec Plus Solution for Injection for Cattle (Italy)

PuAR correct as of 28/11/2018 when RMS was transferred to PT. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0383/001/MR
Name, strength and pharmaceutical form	Animec Super Solution for Injection for Cattle Animec Plus Solución inyectable para bovino (Spain) Animec Plus Solution for Injection for Cattle (Italy)
Applicant	Chanelle Animal Health 7 Rodney Street Liverpool L1 9HZ United Kingdom
Active substance(s)	Ivermectin Clorsulon
ATC Vetcode	QP54AA51
Target species	Cattle
Indication for use	For the treatment of mixed infestation of adult liver fluke and gastro-intestinal roundworms, lungworms, eye worms, and/or mites and lice of beef and non-lactating dairy cattle. **Gastrointestinal Roundworms (adult and fourth-stage larvae):** *Ostertagia* ostertagi (including inhibited larval stages) *O. lyrata* *Haemonchus placei* *Trichostrongylus axei* *T. colubriformis* *Cooperia oncophora* *C. punctata* *C. pectinata* *Bunostomum phlebotomum* *Oesophagostomum radiatum* *Strongyloides papillosus* (adult) *Nematodirus helvetianus* (adult) *Nematodirus spathiger* (adult) *Trichuris* spp. (adult) **Lungworm (adult and fourth-stage larvae):** *Dictyocaulus viviparus* Liver Fluke (adult): *Fasciola hepatica*

	Eye Worms (adult): *Thelazia* spp. **Warbles (parasitic stages):** *Hypoderma bovis* *H. lineatum* **Mange mites:** *Psoroptes bovis* *Sarcoptes scabiei var. Bovis* **Sucking Lice:** *Linognathus vituli* *Haematopinus eurysternus* *Solenopotes capillatus* Animec Super Solution for Injection for Cattle may also be used as an aid in the treatment of biting lice (*Damalinia bovis*) and the mange mite *Chorioptes bovis*, but complete elimination may not occur. **Persistent Activity** Animec Super Solution for Injection for Cattle given at the recommended dosage of 1 ml/50 kg bodyweight controls re-infection with *Haemonchus placei*, *Cooperia* spp. and *Trichostrongylus axei*, acquired up to 14 days after treatment, *Ostertagia ostertagi* and *Oesophagostomum radiatum* acquired up to 21 days after treatment and *Dictyocaulus viviparus* acquired up to 28 days after treatment.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	23 February 2011
Date product first authorised in the Reference Member State (MRP only)	16 April 2010
Concerned Member States for original procedure	Belgium Bulgaria Italy Portugal Romania Slovenia Spain

I. SCIENTIFIC OVERVIEW

Animec Super Solution for Injection for Cattle is authorised for use in cattle. The product is intended for the treatment of mixed trematode and nematode or arthropod infestations in cattle as follows: Gastrointestinal roundworms (adult and fourth larval stages*), Ostertagia ostertagi* (including inhibited larval stages), *Ostertagia lyrata*, *Haemonchus placei*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Cooperia oncophora*, *Cooperia punctata*, *Cooperia pectinata*, *Bunostomum phlebotomum*, *Oesophastamum radiatum*, *Strongyloides papillosus* (adult), *Nematodirus spathiger* (adult), *Nematodirus helvetianus* (adult) and *Trichuris* spp (adult). Treatment of the lungworm (adult and fourth-stage larvae) *Dictylocaulus viviparous* is also indicated, as is treatment of the liver fluke (adult), *Fasciola hepatica*. The eye worm (adult) *Thelazia* spp. may be treated with this product, also the warble fly larvae (parasitic stages) *Hypoderma bovis* and *Hypoderma lineatum*. Mange mites *Psoroptes bovis* and *Sarcoptes scabiei* var. *bovis* may be treated, as may sucking lice spp. *Linognathus vituli*, *Haematopinus eurysternus* and *Solenoptes capillatus*. Animec Super Solution for Injection for Cattle may also be used to treat for biting lice and mange mites *Damalina bovis* and *Chorioptes bovis* respectively, however complete elimination may not occur with these arthropods.

Animec Super Solution for Injection for Cattle, when given at the recommended dose, may be used to control re-infection with *Haemonchus placei*, *Cooperia* spp., and *Trichostrongylus axei* acquired up to fourteen days post treatment. The product may also be used to treat *Ostertagia ostertagi* and *Oesophagostomum radiatum* acquired up to twenty-one days post treatment, and *Dictocaulus viviparous* acquired up to twenty-eight days post treatment.

This application for Animec Super Solution for Injection for Cattle was made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, for a generic application. Bioequivalence is claimed with the reference product, Ivomec Super Injection for Cattle, first authorised in the UK in August 1987.

A single dose of 1 ml per 50 kg bodyweight, which equates to 200 µg ivermectin and 2 mg clorsulon per kg bodyweight, is given. The product is administered to cattle as a subcutaneous injection with doses in excess of 10 ml being divided and administered over different injection sites.

II. QUALITY ASPECTS

A. Composition

The active substances in Animec Super Solution for Inection for Cattle are ivermectin 10 mg/ml and clorsulon 100 mg/ml, and the excipients are glycerol formal, propylene glycol and monoethanolamine.

The containers for Animec Super Solution for Injection for Cattle are composed of high density polyethylene with siliconised grey bromobutyl rubber stopper. The containers are of a 50 ml, 250 ml or 500 ml size.

The choice of formulation is justified.

The product is an established pharmaceutical form and its development has been adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The applicant has provided details of the stages of, and method of manufacture. In process controls have also been described. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

Ivermectin utilised in this product complies with the monograph in the European Pharmacopoeia (Ph. Eur) and conforms to a satisfactory Certificate of Suitability (CEP). Batch analysis data for three batches of ivermectin are analysed on receipt of the active substance from the manufacturer. Each batch is tested for microbial purity, chemistry requirements, identity and solubility. Thereafter, each delivery of ivermectin is tested with regard to description, identity and solubility and one batch per year is subjected to complete testing.

Clorsulon does not have a Ph. Eur monograph. However, an acceptable monograph from the United States Pharmacopoeia was presented, against which this active substance is tested.

The excipients are glycerol formal, propylene glycol and monoethanolamine. For propylene glycol, a Ph. Eur monograph exists and the British Pharmacopoeial monograph for ethanolamine is used for monoethanolamine. Glycerol formal does not have a pharmacopoeial monograph, an in-house specification was developed for this excipient.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

There are no intermediate products.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided.

G. Stability

Active substance:
A certificate of suitability (CEP) for ivermectin states a retest interval of three years when stored in a double-lined heat-sealed polyethylene bag within an aluminium tin. Data regarding the stability of clorsulon are provided in an EDMF (European Drug Masterfile) provided by the manufacturer. For clorsulon, data were included on three batches prepared by different means, stored for six months and twenty-four months at 40°C/75% RH, and at thirty-six months at 25°C/60% RH. Containers were representative of commercial packaging. Data were satisfactory and a retest interval of two years was justified.

Finished product:
Two batches of finished product contained in each proposed pack size were subjected to testing under VICH[1] long term and accelerated conditions. Conditions were 25°C/60% RH and 40°C/75% RH. Some sensitivity to light was detected with regard to ivermectin, thus it is recommended in the SPC that the product is protected from light and stored in the outer carton. The shelf-life of the finished product as packaged for sale is three years.

In-Use:
Data were provided on one batch of Animec Super Solution for Injection for Cattle in 50 ml packs, and on two batches of product contained in 500 ml packs. Stability studies demonstrated that no deterioration in the product was seen that

[1] International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

would curtail the proposed twenty-eight day in-use shelf life. Any unused product should be discarded.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Special precautions for storage:

- Protect from light.
- Keep the container in the outer carton in order to protect from light.

Shelf-life:

- Shelf life of the veterinary medicinal product as packaged for sale: 3 years
- Shelf-life after first opening the immediate packaging: Following withdrawal of the first dose, use the product within 28 days. Discard unused material.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Animec Super Solution for Injection for Cattle is a generic product based on the reference product Ivomec Super Injection for Cattle.

III.A Safety Testing

Pharmacological Studies

This was a generic application in accordance with Directive 2004/82/EC as amended, and as such there was no requirement to submit data for this section.

Toxicological Studies

This was a generic application in accordance with Directive 2004/82/EC as amended, and as such there was no requirement to submit data for this section.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

User safety warnings are as follows:

- Do not eat, drink or smoke whilst handling the product.
- Wash hands after use.
- Direct contact with the skin should be avoided.
- Take care to avoid self-injection: the product may cause local irritation and/or pain at the site of injection. In case of accidental self injection, seek medical advice and show the label to the doctor.

Ecotoxicity

Animec Super Solution for Injection for Cattle is an injectable solution containing 10 mg/ml ivermectin and 100 mg/ml clorsulon. The product is most likely to be used as a single treatment in mid-winter, when cattle are contained in housing. This may be followed by a second dose at turnout in May; however, a second dose is considered a worst case scenario and would be unlikely to occur unless there was a problem on a specific farm. A Phase II risk assessment was required because the product is offered as an anti-parasitic for use in pasture animals. Ivermectin and clorsulon residues reach the environment via the manure from housed animals, which are spread onto pasture.

Ivermectin is poorly metabolised and is excreted mainly in the faeces, which in this case is spread onto soil. The applicant provided published data with regard

to the effect of ivermectin on non-target species. In addition, PEC[2] values for a variety of parameters were provided by the applicant, with subsequent PNEC[3] values provided for soil, earthworms, algae, soil micro-organisms, fish sediment organisms, dung fly and dung beetle larvae. Comparison of PNECs using the worst case scenario PEC demonstrated that ivermectin does not pose a threat to the environment at Tier A. There is however a risk to aquatic organisms. The PEC_{soil} was calculated for animals in housing, and was deemed to be 1.5 ug/kg where 0.2 mg/kg/bodyweight ivermectin is given as a single administration. Tier B assessment of dung beetles suggests that as cattle are housed when treated, there is not a direct threat to these organisms, which do not generally reside within housing. Suitable wording in the Summary of Product Characteristics (SPC) ensures the protection of fish and aquatic life.

Clorsulon is also poorly metabolised in cattle, with the majority of the active substance being excreted in the faeces after seven days. PNEC values for clorsulon, provided for algae, fish, daphnia, dung fly larvae and earthworms are within the acceptable range, with comparison of PNECs using the worst case scenario PEC values all giving <1. Thus clorsulon is not expected to pose an environmental risk. Again, supplemental data in the form of referenced material provided supporting data for the use of clorsulon in Animec Super Solution for Injection for Cattle.

Finally, the risk of using both compounds together was evaluated and found to be acceptable.

[2] Predicted Environmental Concentration
[3] Predicted No Effect Concentration

III.B Residues documentation

Residue Studies

The CVMP have adopted an opinion following an article 35 referral for injectable medicinal products with regard to the withdrawal period for injectable products containing ivermectin in combination with clorsulon. With regard to this Commission decision, reference to a residue study was not required.

MRLs

Pharmacologically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissue**	**Other provisions**
Ivermectin	22,23-Dihydroavermectin B1a	All food producing mammals	100 ug/kg 30 ug/kg 100 ug/kg	Liver Kidney Fat	Not for use in animals producing milk for human consumption
Clorsulon	Clorsulon	Bovine	200 ug/kg 100 ug/kg 35 ug/kg	Kidney Liver Muscle	

Withdrawal Periods

Meat and offal: 66 days
Milk: Do not use in cattle producing milk for human consumption.
Do not use in non-lactating dairy cows including pregnant heifers within 60 days of calving.

IV CLINICAL ASSESSMENT (EFFICACY)

Bioequivalence of Animec Super Solution for Injection for Cattle with Ivomec Super Injection for Cattle was claimed. A bioequivalence study was presented conforming to GLP[4], which compared Ivomec Super Injection for Cattle and Animec Super Solution for Injection for Cattle.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Pharmacodynamic data for the two active substances of Animec Super Solution for Injection for Cattle were not required. Relevant information for the reference product, submitted by the applicant, were considered appropriate.

Pharmacokinetics

A two-way, single dose GLP compliant bioequivalence study compared Animec Super Solution for Injection for Cattle with Ivomec Super Injection for Cattle. Both products were administered by subcutaneous injection. A suitable number of cattle were divided into treatment groups and subsequently injected with either the test product or the reference product at a rate of 0.2 mg/kg ivermectin and 2.0 mg/kg clorsulon per dose. Prior to administration, the animals were acclimatised and examined, then subjected to baseline blood testing and weighing. Blood sampling was also performed during the trial, with plasma levels of both test and reference product being compared with regard to active substances and residues content. Primary parameters used in statistical evaluation were AUC_t[5] and C_{max}[6]. Bioequivalence was established with a 90% confidence interval for the combined, standard equivalence limits of between 80%-125% for both AUC_t and C_{max}. The level of significance was established as being $p< 0.05$. Pharmacokinetic parameters were established via analysis of variance (ANOVA), and a 90% confidence interval based on Wilcoxon's Rank Sum Test was calculated for T_{max}.

No adverse reactions were noted during the trial; however some slight swelling occurred around the injection sites. Plasma levels of ivermectin and clorsulon for Animec Super Solution for Injection for Cattle during and after treatment closely reflected those of the reference product. Animec Super Solution for Injection for Cattle and Ivomec Super Injection for cattle were therefore considered to be bioequivalent with regard to pharmacokinetic parameters.

Resistance

Not applicable.

[4] Good Laboratory Practice
[5] Area under the curve with respect to time.
[6] Peak serum concentration of the therapeutic drug

IV.B Clinical Studies

Animec Super Solution for Injection for Cattle was established as being bioequivalent to the reference product, Ivomec Super Injection for Cattle. The efficacy of the generic product was therefore determined with no requirement by the applicant to provide further toxicological or pharmacological tests. Contraindications and warnings are the same as those provided in the SPC for the reference product.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)